

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PENNSYLVANIA EMPLOYEE BENEFIT TRUST FUND, on behalf of itself and all others similarly situated, JOSEPH MACKEN, and COMMISSIONER LINDA A. WATTERS,

Civ. No. 05-075-SLR
(Lead Case)

Plaintiffs,

v.

ZENECA, INC. and ASTRAZENECA PHARMACEUTICALS, L.P.,

Defendants.

**APPENDIX FILED IN SUPPORT OF
PLAINTIFFS' BRIEF IN OPPOSITION TO DEFENDANTS' MOTION TO DISMISS**

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August 5, 2005

Plaintiffs respectfully submit this Appendix in Support of their Brief in opposition to Defendants' Motion to Dismiss.

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LEXSTAT 21 CFR 201.5

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*** THIS SECTION IS CURRENT THROUGH THE JULY 28, 2005 ISSUE OF ***
*** THE FEDERAL REGISTER ***

TITLE 21 -- FOOD AND DRUGS
CHAPTER I -- FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN
SERVICES
SUBCHAPTER C -- DRUGS: GENERAL
PART 201 -- LABELING
SUBPART A -- GENERAL LABELING PROVISIONS

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21 CFR 201.5

§ 201.5 Drugs; adequate directions for use.

"Adequate directions for use" means directions under which the layman can use a drug safely and for the purposes for which it is intended. (Section 201.128 defines "intended use.") Directions for use may be inadequate because, among other reasons, of omission, in whole or in part, or incorrect specification of:

- (a) Statements of all conditions, purposes, or uses for which such drug is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the drug is commonly used; except that such statements shall not refer to conditions, uses, or purposes for which the drug can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner.
- (b) Quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and different physical conditions.
- (c) Frequency of administration or application.
- (d) Duration of administration or application.
- (e) Time of administration or application (in relation to time of meals, time of onset of symptoms, or other time factors).
- (f) Route or method of administration or application.
- (g) Preparation for use, i.e., shaking, dilution, adjustment of temperature, or, other manipulation or process.

HISTORY: [41 FR 6908, Feb. 13, 1976]

AUTHORITY: AUTHORITY NOTE APPLICABLE TO ENTIRE PART:
21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

NOTES: NOTES APPLICABLE TO ENTIRE TITLE:

Cross References: Food Safety and Inspection Services, Department of Agriculture: See Meat and Poultry Inspection, 9 CFR CHAPTER III.

Federal Trade Commission: See Commercial Practices, 16 CFR chapter I.

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U.S. Customs Service, Department of the Treasury: See Customs Duties, 19 CFR chapter I.
Internal Revenue Service, Department of the Treasury: See Internal Revenue, 26 CFR chapter I.
Bureau of Alcohol, Tobacco, and Firearms, Department of the Treasury: See Alcohol, Tobacco Production and Firearms, 27 CFR chapter I.

NOTES APPLICABLE TO ENTIRE CHAPTER:

[PUBLISHER'S NOTE NOTE: Nomenclature changes affecting chapter I appear at: *70 FR 40880*, July 15, 2005.]

[PUBLISHER'S NOTE: For the uniform compliance date for food labeling regulations under Chapter 1, see *61 FR 67710*, Dec. 24, 1996; *61 FR 68145*, Dec. 27, 1996; *62 FR 49881*, Sept. 23, 1997.]

NOTES APPLICABLE TO ENTIRE PART:

[PUBLISHER'S NOTE: Nomenclature changes affecting part 201 appear at *68 FR 24879*, May 9, 2003; *69 FR 13716*, *13717*, Mar. 24, 2004.]

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LEXSTAT 21 CFR 201.57

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*** THIS SECTION IS CURRENT THROUGH THE JULY 28, 2005 ISSUE OF ***
*** THE FEDERAL REGISTER ***

TITLE 21 -- FOOD AND DRUGS
CHAPTER I -- FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN
SERVICES
SUBCHAPTER C -- DRUGS: GENERAL
PART 201 -- LABELING
SUBPART B -- LABELING REQUIREMENTS FOR PRESCRIPTION DRUGS AND/OR INSULIN

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21 CFR 201.57

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

(a) "Description": (1) Under this section heading, the labeling shall contain:

- (i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;
- (ii) The type of dosage form and the route of administration to which the labeling applies;
- (iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for labels;
- (iv) If the product is sterile, a statement of that fact;
- (v) The pharmacological or therapeutic class of the drug;
- (vi) The chemical name and structural formula of the drug;

(vii) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(2) If appropriate, other important chemical or physical information, such as physical constants, or pH, shall be stated.

(b) "Clinical Pharmacology": (1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information.

(2) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section of the labeling only under the following circumstances:

(i) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown."

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.126(b) of this chapter.

(c) "Indications and Usage": (1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

(iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(d) "Contraindications": Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their par-

ticular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state "None known."

(e) "Warnings": Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

(f) "Precautions": Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

(1) General: This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other specific section or subsection of the labeling.

(2) Information for patients: This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the "Precautions" section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in § 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling.

(3) Laboratory tests: This subsection of the labeling shall identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information shall be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be done before, during, and after therapy.

(4)(i) Drug interactions: This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the "Dosage and Administration" section of the labeling rather than under this subsection of the labeling.

(ii) Drug/laboratory test interactions: This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) Carcinogenesis, mutagenesis, impairment of fertility: This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information

shall be included under the "Warnings" section of the labeling. Also, under "Precautions," the labeling shall state: "See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility."

(6) Pregnancy: This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling shall contain the following information:

(i) Teratogenic effects. Under this heading the labeling shall identify one of the following categories that applies to the drug, and the labeling shall bear the statement required under the category:

(a) Pregnancy category A. If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category A. Studies in pregnant women have not shown that (name of drug) increases the risk of fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to demonstrate a risk to the fetus, the labeling shall also state: "Reproduction studies have been performed in (kinds of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug)." The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(b) Pregnancy category B. If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling shall state: "Pregnancy Category B. Reproduction studies have been performed in (kind(s) of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category B. Reproduction studies in (kind(s) of animal(s)) have shown (describe findings) at (x) times the human dose. Studies in pregnant women, however, have not shown that (name of drug) increases the risk of abnormalities when administered during the first (second, third, or all) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (name of drug) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(c) Pregnancy category C. If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: "Pregnancy Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed." The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(d) Pregnancy category D. If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: "Pregnancy Category D. See 'Warnings' section." Under the "Warnings" section, the labeling states: "(Name of drug) can cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) If this drug is

used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(e) Pregnancy category X. If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: "Pregnancy Category X. See 'Contraindications' section." Under "Contraindications," the labeling shall state: "(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(ii) Nonteratogenic effects. Under this heading the labeling shall contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading shall include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(7) Labor and delivery: If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling shall describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, this subsection of the labeling shall state that the information is unknown.

(8) Nursing mothers: (i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

(ii) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling shall state: "Because of the potential for serious adverse reactions in nursing infants from (name of drug) (or, "Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "Caution should be exercised when (name of drug) is administered to a nursing woman."

(iii) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (name of drug) (or, "Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (name of drug) is administered to a nursing woman."

(9) Pediatric use: (i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this section, the terms "pediatric population(s)" and "pediatric patient(s)" are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(ii) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the "Indications and Usage" section of the labeling, and appropriate pediatric dosage information shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection shall cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related

to the safe and effective pediatric use of the drug. Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical Studies" section. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(ii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling shall contain either the following statement, or a reasonable alternative: "The safety and effectiveness of (drug name) have been established in the age groups - to - (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population)." Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions shall be included in the "Dosage and Administration" section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings," "Precautions," and "Dosage and Administration" sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection of the labeling shall contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (-) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

(vi) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

(vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(viii) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made, generally in the "Contraindications," "Warnings," or "Precautions" section.

(10) Geriatric use. (i) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population shall be described under the "Indications and Usage" section of the labeling, and appropriate geriatric dosage shall be stated under the "Dosage and Administration" section of the labeling. The "Geriatric use" subsection shall cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection of the labeling shall pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling shall be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information shall also be contained in "Contraindications," "Warnings," and elsewhere in "Precautions."

(ii) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, shall be contained in the "Geriatric use" subsection and shall reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biological license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection shall contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(A) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection shall include the following statement:

"Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."

(B) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection shall contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), -- percent were 65 and over, while -- percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(C) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection of the labeling shall contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, shall refer to more detailed discussions in the "Contraindications," "Warnings," "Dosage and Administration," or other sections of the labeling.

(iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the "Geriatric use" subsection of the labeling and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" section and "Drug interactions" subsection of the "Precautions" section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs.

(B) If a drug is known to be substantially excreted by the kidney, the "Geriatric use" subsection shall include the statement:

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"This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."

(iv) If use of the drug in the elderly appears to cause a specific hazard, the hazard shall be described in the "Geriatric use" subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications," "Warnings," or "Precautions" section of the labeling, and the "Geriatric use" subsection shall refer to those sections.

(v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

"Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely."

(vi) If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(g) "Adverse Reactions": An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to (name of drug) is (are) (list reactions). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (list reactions), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (list reactions)." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(h) "Drug Abuse and Dependence": Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) Controlled Substance: If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) Abuse: This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

(3) Dependence: This subsection of the labeling shall describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and shall identify the quantity of the drug over a period of time

that may lead to tolerance or dependence, or both. Details shall be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state shall be provided, and the principles of treating the effects of abrupt withdrawal shall be described.

(i) "Overdosage": Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

- (1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.
- (2) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis).

(3) Oral LD[50] of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses.

(4) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life-threatening.

- (5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(j) "Dosage and Administration": This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

(k) "How Supplied": This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

- (1) The strength of the dosage form, e.g., 10-milligram tablets, in metric system and, if the apothecary system is used, a statement of the strength is placed in parentheses after the metric designation;
- (2) The units in which the dosage form is ordinarily available for prescribing by practitioners, e.g., bottles of 100;
- (3) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code; and
- (4) Special handling and storage conditions.

(l) "Animal Pharmacology and/or Animal Toxicology": In most cases, the labeling need not include this section. Significant animal data necessary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is

administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(m) "Clinical Studies" and "References": These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the "Clinical Studies" or "References" section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for use of the drug, the reference shall be based upon, or the clinical study shall constitute, an adequate and well-controlled clinical investigation under § 314.126(b) of this chapter.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks shall also be identified or discussed in the appropriate section of the labeling for the drug.

HISTORY: [44 FR 37462, June 26, 1979, as amended at 55 FR 11576, March 29, 1990, 59 FR 64249, Dec. 13, 1994; 62 FR 45313, 45325, Aug. 27, 1997; 63 FR 66378, 66396, Dec. 1, 1998]

AUTHORITY: AUTHORITY NOTE APPLICABLE TO ENTIRE PART:

21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

NOTES: NOTES APPLICABLE TO ENTIRE TITLE:

Cross References: Food Safety and Inspection Services, Department of Agriculture: See Meat and Poultry Inspection, 9 CFR CHAPTER III.

Federal Trade Commission: See Commercial Practices, 16 CFR chapter I.

U.S. Customs Service, Department of the Treasury: See Customs Duties, 19 CFR chapter I.

Internal Revenue Service, Department of the Treasury: See Internal Revenue, 26 CFR chapter I.

Bureau of Alcohol, Tobacco, and Firearms, Department of the Treasury: See Alcohol, Tobacco Production and Firearms, 27 CFR chapter I.

NOTES APPLICABLE TO ENTIRE CHAPTER:

[PUBLISHER'S NOTE NOTE: Nomenclature changes affecting chapter I appear at: 70 FR 40880, July 15, 2005.]

[PUBLISHER'S NOTE: For the uniform compliance date for food labeling regulations under Chapter I, see 61 FR 67710, Dec. 24, 1996; 61 FR 68145, Dec. 27, 1996; 62 FR 49881, Sept. 23, 1997.]

NOTES APPLICABLE TO ENTIRE PART:

[PUBLISHER'S NOTE: Nomenclature changes affecting part 201 appear at 68 FR 24879, May 9, 2003; 69 FR 13716, 13717, Mar. 24, 2004.]

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*** THIS SECTION IS CURRENT THROUGH THE JULY 28, 2005 ISSUE OF ***
*** THE FEDERAL REGISTER ***

TITLE 21 -- FOOD AND DRUGS
CHAPTER I -- FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D -- DRUGS FOR HUMAN USE
PART 314 -- APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG
SUBPART B -- APPLICATIONS

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21 CFR 314.50

§ 314.50 Content and format of an application.

Applications and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Three copies of the application are required: An archival copy, a review copy, and a field copy. An application for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. Other applications will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an application of the type described in section 505(b)(2) of the act, an amendment, and a supplement. The application is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source. FDA will maintain guidance documents on the format and content of applications to assist applicants in their preparation.

(a) Application form. The applicant shall submit a completed and signed application form that contains the following:

(1) The name and address of the applicant; the date of the application; the application number if previously issued (for example, if the application is a resubmission, an amendment, or a supplement); the name of the drug product, including its established, proprietary, code, and chemical names; the dosage form and strength; the route of administration; the identification numbers of all investigational new drug applications that are referenced in the application; the identification numbers of all drug master files and other applications under this part that are referenced in the application; and the drug product's proposed indications for use.

(2) A statement whether the submission is an original submission, a 505(b)(2) application, a resubmission, or a supplement to an application under § 314.70.

(3) A statement whether the applicant proposes to market the drug product as a prescription or an over-the-counter product.

(4) A check-list identifying what enclosures required under this section the applicant is submitting.

(5) The applicant, or the applicant's attorney, agent, or other authorized official shall sign the application. If the person signing the application does not reside or have a place of business within the United States, the application is

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required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(b) **Index.** The archival copy of the application is required to contain a comprehensive index by volume number and page number to the summary under paragraph (c) of this section, the technical sections under paragraph (d) of this section, and the supporting information under paragraph (f) of this section.

(c) **Summary.** (1) An application is required to contain a summary of the application in enough detail that the reader may gain a good general understanding of the data and information in the application, including an understanding of the quantitative aspects of the data. The summary is not required for supplements under § 314.70. Resubmissions of an application should contain an updated summary, as appropriate. The summary should discuss all aspects of the application, and synthesize the information into a well-structured and unified document. The summary should be written at approximately the level of detail required for publication in, and meet the editorial standards generally applied by, refereed scientific and medical journals. In addition to the agency personnel reviewing the summary in the context of their review of the application, FDA may furnish the summary to FDA advisory committee members and agency officials whose duties require an understanding of the application. To the extent possible, data in the summary should be presented in tabular and graphic forms. FDA has prepared a guideline under § 10.90(b) that provides information about how to prepare a summary. The summary required under this paragraph may be used by FDA or the applicant to prepare the Summary Basis of Approval document for public disclosure (under § 314.430(e)(2)(ii)) when the application is approved.

(2) The summary is required to contain the following information:

(i) The proposed text of the labeling, including, if applicable, any Medication Guide required under part 208 of this chapter, for the drug, with annotations to the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling, and, if the application is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57 of this chapter.

(ii) A statement identifying the pharmacologic class of the drug and a discussion of the scientific rationale for the drug, its intended use, and the potential clinical benefits of the drug product.

(iii) A brief description of the marketing history, if any, of the drug outside the United States, including a list of the countries in which the drug has been marketed, a list of any countries in which the drug has been withdrawn from marketing for any reason related to safety or effectiveness, and a list of countries in which applications for marketing are pending. The description is required to describe both marketing by the applicant and, if known, the marketing history of other persons.

(iv) A summary of the chemistry, manufacturing, and controls section of the application.

(v) A summary of the nonclinical pharmacology and toxicology section of the application.

(vi) A summary of the human pharmacokinetics and bioavailability section of the application.

(vii) A summary of the microbiology section of the application (for anti-infective drugs only).

(viii) A summary of the clinical data section of the application, including the results of statistical analyses of the clinical trials.

(ix) A concluding discussion that presents the benefit and risk considerations related to the drug, including a discussion of any proposed additional studies or surveillance the applicant intends to conduct postmarketing.

(d) **Technical sections.** The application is required to contain the technical sections described below. Each technical section is required to contain data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the application or whether grounds exist under section 505(d) of the act to refuse to approve the application. The required technical sections are as follows:

(1) Chemistry, manufacturing, and controls section. A section describing the composition, manufacture, and specification of the drug substance and the drug product, including the following:

(i) Drug substance. A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the

identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, tests, analytical procedures, and acceptance criteria relating to stability, sterility, particle size, and crystalline form. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, and analytical procedures. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(ii)(a) Drug product. A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product) and a statement of the composition of the drug product; the specifications for each component; the name and address of each manufacturer of the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, including, for example, tests, analytical procedures, and acceptance criteria relating to sterility, dissolution rate, container closure systems; and stability data with proposed expiration dating. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls, and analytical procedures. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(b) Unless provided by paragraph (d)(1)(ii)(a) of this section, for each batch of the drug product used to conduct a bioavailability or bioequivalence study described in § 320.38 or § 320.63 of this chapter or used to conduct a primary stability study: The batch production record; the specification for each component and for the drug product; the names and addresses of the sources of the active and noncompendial inactive components and of the container and closure system for the drug product; the name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility; and the results of any test performed on the components used in the manufacture of the drug product as required by § 211.84(d) of this chapter and on the drug product as required by § 211.165 of this chapter.

(c) The proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product.

(iii) Environmental impact. The application is required to contain either a claim for categorical exclusion under § 25.30 or 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter.

(iv) The applicant may, at its option, submit a complete chemistry, manufacturing, and controls section 90 to 120 days before the anticipated submission of the remainder of the application. FDA will review such early submissions as resources permit.

(v) The applicant shall include a statement certifying that the field copy of the application has been provided to the applicant's home FDA district office.

(2) Nonclinical pharmacology and toxicology section. A section describing, with the aid of graphs and tables, animal and in vitro studies with drug, including the following:

(i) Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.

(ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use.

(iii) Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.

(iv) Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.

(v) For each nonclinical laboratory study subject to the good laboratory practice regulations under Part 58 a statement that it was conducted in compliance with the good laboratory practice regulations in Part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(3) Human pharmacokinetics and bioavailability section. A section describing the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the submission of in vivo bioavailability data under Subpart B of Part 320, including the following:

(i) A description of each of the bioavailability and pharmacokinetic studies of the drug in humans performed by or on behalf of the applicant that includes a description of the analytical procedures and statistical methods used in each study and a statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in Part 50.

(ii) If the application describes in the chemistry, manufacturing, and controls section tests, analytical procedures, and acceptance criteria needed to assure the bioavailability of the drug product or drug substance, or both, a statement in this section of the rationale for establishing the tests, analytical procedures, and acceptance criteria, including data and information supporting the rationale.

(iii) A summarizing discussion and analysis of the pharmacokinetics and metabolism of the active ingredients and the bioavailability or bioequivalence, or both, of the drug product.

(4) Microbiology section. If the drug is an anti-infective drug, a section describing the microbiology data, including the following:

(i) A description of the biochemical basis of the drug's action on microbial physiology.

(ii) A description of the antimicrobial spectra of the drug, including results of in vitro preclinical studies to demonstrate concentrations of the drug required for effective use.

(iii) A description of any known mechanisms of resistance to the drug, including results of any known epidemiologic studies to demonstrate prevalence of resistance factors.

(iv) A description of clinical microbiology laboratory procedures (for example, in vitro sensitivity discs) needed for effective use of the drug.

(5) Clinical data section. A section describing the clinical investigations of the drug, including the following:

(i) A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.

(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this is to be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study.

(iii) A description of each uncontrolled clinical study, a summary of the results, and a brief statement explaining why the study is classified as uncontrolled.

(iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended. The effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease, also shall be presented.

(vi) A summary and updates of safety information, as follows:

(a) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data shall be presented by gender, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also shall be presented, such as for patients with renal failure or patients with differ-

ent levels of severity of the disease. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

(b) The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(a) of this section. In addition, the reports are required to include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant shall submit these reports (1) 4 months after the initial submission; (2) following receipt of an approvable letter; and (3) at other times as requested by FDA. Prior to the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

(vii) If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

(viii) An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

(ix) A statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

(x) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer -- in lieu of a listing of the specific obligations transferred -- may be submitted.

(xi) If original subject records were audited or reviewed by the sponsor in the course of monitoring any clinical study to verify the accuracy of the case reports submitted to the sponsor, a list identifying each clinical study so audited or reviewed.

(6) Statistical section. A section describing the statistical evaluation of clinical data, including the following:

(i) A copy of the information submitted under paragraph (d)(5)(ii) of this section concerning the description and analysis of each controlled clinical study, and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies.

(ii) A copy of the information submitted under paragraph (d)(5)(vi)(a) of this section concerning a summary of information about the safety of the drug product, and the documentation and supporting statistical analyses used in evaluating the safety information.

(7) Pediatric use section. A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under § 314.55.

(e) Samples and labeling.

(1) Upon request from FDA, the applicant shall submit the samples described below to the places identified in the agency's request. FDA will generally ask applicants to submit samples directly to two or more agency laboratories that will perform all necessary tests on the samples and validate the applicant's analytical procedures.

(i) Four representative samples of the following, each sample in sufficient quantity to permit FDA to perform three times each test described in the application to determine whether the drug substance and the drug product meet the specifications given in the application:

(a) The drug product proposed for marketing;

- (b) The drug substance used in the drug product from which the samples of the drug product were taken; and
- (c) Reference standards and blanks (except that reference standards recognized in an official compendium need not be submitted).
 - (ii) Samples of the finished market package, if requested by FDA.

(2) The applicant shall submit the following in the archival copy of the application:

- (i) Three copies of the analytical procedures and related descriptive information contained in the chemistry, manufacturing, and controls section under paragraph (d)(1) of this section for the drug substance and the drug product that are necessary for FDA's laboratories to perform all necessary tests on the samples and to validate the applicant's analytical procedures. The related descriptive information includes a description of each sample; the proposed regulatory specifications for the drug; a detailed description of the procedures of analysis; supporting data for accuracy, specificity, precision and ruggedness; and complete results of the applicant's tests on each sample.
- (ii) Copies of the label and all labeling for the drug product (including, if applicable, any Medication Guide required under part 208 of this chapter) for the drug product (4 copies of draft labeling or 12 copies of final printed labeling).

(f) Case report forms and tabulations. The archival copy of the application is required to contain the following case report tabulations and case report forms:

- (1) Case report tabulations. The application is required to contain tabulations of the data from each adequate and well-controlled study under § 314.126 (Phase 2 and Phase 3 studies as described in §§ 312.21 (b) and (c) of this chapter), tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in § 312.21(a) of this chapter), and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. The tabulations are required to include the data on each patient in each study, except that the applicant may delete those tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. Barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during the conduct of FDA's review of the application. If such unforeseen circumstances do occur, any request for deleted tabulations will be made by the director of the FDA division responsible for reviewing the application, in accordance with paragraph (f)(3) of this section.
- (2) Case report forms. The application is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo. This requirement may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study.
- (3) Additional data. The applicant shall submit to FDA additional case report forms and tabulations needed to conduct a proper review of the application, as requested by the director of the FDA division responsible for reviewing the application. The applicant's failure to submit information requested by FDA within 30 days after receipt of the request may result in the agency viewing any eventual submission as a major amendment under § 314.60 and extending the review period as necessary. If desired by the applicant, the FDA division director will verify in writing any request for additional data that was made orally.
- (4) Applicants are invited to meet with FDA before submitting an application to discuss the presentation and format of supporting information. If the applicant and FDA agree, the applicant may submit tabulations of patient data and case report forms in a form other than hard copy, for example, on microfiche or computer tapes.
- (g) Other. The following general requirements apply to the submission of information within the summary under paragraph (c) of this section and within the technical sections under paragraph (d) of this section.
- (1) The applicant ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously is required to identify the file by name, reference number, volume, and page number in the agency's records where the information can be found. A reference to information submitted to the agency by a person other than the applicant is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(2) The applicant shall submit an accurate and complete English translation of each part of the application that is not in English. The applicant shall submit a copy of each original literature publication for which an English translation is submitted.

(3) If an applicant who submits a new drug application under section 505(b) of the act obtains a "right of reference or use," as defined under § 314.3(b), to an investigation described in clause (A) of section 505(b)(1) of the act, the applicant shall include in its application a written statement signed by the owner of the data from each such investigation that the applicant may rely on in support of the approval of its application, and provide FDA access to, the underlying raw data that provide the basis for the report of the investigation submitted in its application.

(h) Patent information. The application is required to contain the patent information described under § 314.53.

(i) Patent certification -- (1) Contents. A 505(b)(2) application is required to contain the following:

(i) Patents claiming drug, drug product, or method of use. (A) Except as provided in paragraph (i)(2) of this section, a certification with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims a drug (the drug product or drug substance that is a component of the drug product) on which investigations that are relied upon by the applicant for approval of its application were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the act and § 314.53. For each such patent, the applicant shall provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(1) That the patent information has not been submitted to FDA. The applicant shall entitle such a certification "Paragraph I Certification";

(2) That the patent has expired. The applicant shall entitle such a certification "Paragraph II Certification";

(3) The date on which the patent will expire. The applicant shall entitle such a certification "Paragraph III Certification"; or

(4) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. The applicant shall entitle such a certification "Paragraph IV Certification". This certification shall be submitted in the following form:

I, (name of applicant), certify that Patent No. (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this application is submitted.

The certification shall be accompanied by a statement that the applicant will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(c) with respect to the content of the notice.

(B) If the drug on which investigations that are relied upon by the applicant were conducted is itself a licensed generic drug of a patented drug first approved under section 505(b) of the act, the appropriate patent certification under this section with respect to each patent that claims the first-approved patented drug or that claims an approved use for such a drug.

(ii) No relevant patents. If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (i)(1)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

(iii) Method of use patent. (A) If information that is submitted under section 505(b) or (c) of the act and § 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication that, according to the patent information submitted under section 505(b) or (c) of the act and § 314.53 or in the opinion of the applicant, is claimed by a use patent, the applicant shall submit an applicable certification under paragraph (i)(1)(i) of this section.

(2) Method of manufacturing patent. An applicant is not required to make a certification with respect to any patent that claims only a method of manufacturing the drug product for which the applicant is seeking approval.

(3) Licensing agreements. If a 505(b)(2) application is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant shall submit a certification under paragraph (i)(1)(i)(A)(4) of this section ("Paragraph IV Certification") as to that patent and a statement that it has been granted a patent license. If the patent owner consents to an immediate effective date upon approval of the 505(b)(2) application, the application shall contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to an immediate effective date.

(4) Late submission of patent information. If a patent described in paragraph (i)(1)(i)(A) of this section is issued and the holder of the approved application for the patented drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted a 505(b)(2) application that, before the submission of the patent information, contained an appropriate patent certification is not required to submit an amended certification. An applicant whose 505(b)(2) application is filed after a late submission of patent information or whose 505(b)(2) application was previously filed but did not contain an appropriate patent certification at the time of the patent submission shall submit a certification under paragraph (i)(1)(i) or (i)(1)(ii) of this section or a statement under paragraph (i)(1)(iii) of this section as to that patent.

(5) Disputed patent information. If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn or changed, the applicant must submit an appropriate certification for each relevant patent.

(6) Amended certifications. A certification submitted under paragraphs (i)(1)(i) through (i)(1)(iii) of this section may be amended at any time before the effective date of the approval of the application. An applicant shall submit an amended certification as an amendment to a pending application or by letter to an approved application. If an applicant with a pending application voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. Once an amendment or letter for the change in certification has been submitted, the application will no longer be considered to be one containing the prior certification.

(i) After finding of infringement. An applicant who has submitted a certification under paragraph (i)(1)(i)(A)(4) of this section and is sued for patent infringement within 45 days of the receipt of notice sent under § 314.52 shall amend the certification if a final judgment in the action is entered finding the patent to be infringed unless the final judgment also finds the patent to be invalid. In the amended certification, the applicant shall certify under paragraph (i)(1)(i)(A)(3) of this section that the patent will expire on a specific date.

(ii) After removal of a patent from the list. If a patent is removed from the list, any applicant with a pending application (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent shall amend its certification. The applicant shall certify under paragraph (i)(1)(ii) of this section that no patents described in paragraph (i)(1)(i) of this section claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents. In the amendment, the applicant shall state the reason for the change in certification (that the patent is or has been removed from the list). A patent that is the subject of a lawsuit under § 314.107(c) shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended. An applicant shall submit an amended certification as an amendment to a pending application. Once an amendment for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (i)(1)(i)(A)(4) of this section.

(iii) Other amendments. (A) Except as provided in paragraphs (i)(4) and (i)(6)(iii)(B) of this section, an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate.

(B) An applicant is not required to amend a submitted certification when information on an otherwise applicable patent is submitted after the effective date of approval for the 505(b)(2) application.

(j) Claimed exclusivity. A new drug product, upon approval, may be entitled to a period of marketing exclusivity under the provisions of § 314.108. If an applicant believes its drug product is entitled to a period of exclusivity, it shall submit with the new drug application prior to approval the following information:

- (1) A statement that the applicant is claiming exclusivity.
- (2) A reference to the appropriate paragraph under § 314.108 that supports its claim.
- (3) If the applicant claims exclusivity under § 314.108(b)(2), information to show that, to the best of its knowledge or belief, a drug has not previously been approved under section 505(b) of the act containing any active moiety in the drug for which the applicant is seeking approval.
- (4) If the applicant claims exclusivity under § 314.108(b)(4) or (b)(5), the following information to show that the application contains "new clinical investigations" that are "essential to approval of the application or supplement" and were "conducted or sponsored by the applicant":
 - (i) "New clinical investigations." A certification that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in § 314.108(a).
 - (ii) "Essential to approval." A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval, a certification that the applicant has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the application, and an explanation as to why the studies or reports are insufficient.
 - (iii) "Conducted or sponsored by." If the applicant was the sponsor named in the Form FDA-1571 for an investigational new drug application (IND) under which the new clinical investigation(s) that is essential to the approval of its application was conducted, identification of the IND by number. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its application, and information supporting the certification. To demonstrate "substantial support," an applicant must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation of why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.
- (k) Financial certification or disclosure statement. The application shall contain a financial certification or disclosure statement or both as required by part 54 of this chapter.
- (l) Format of an original application. (1) Archival copy. The applicant must submit a complete archival copy of the application that contains the information required under paragraphs (a) through (f) of this section. FDA will maintain the archival copy during the review of the application to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application, to give other agency personnel access to the application for official business, and to maintain in one place a complete copy of the application. Except as required by paragraph (l)(1)(i) of this section, applicants may submit the archival copy on paper or in electronic format provided that electronic submissions are made in accordance with part 11 of this chapter.
 - (i) Labeling. The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (l)(5) of this section. This requirement is in addition to the requirements of paragraph (e)(2)(ii) of this section that copies of the formatted label and all labeling be submitted. Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.
 - (ii) [Reserved]
- (2) Review copy. The applicant must submit a review copy of the application. Each of the technical sections, described in paragraphs (d)(1) through (d)(6) of this section, in the review copy is required to be separately bound with a copy of the application form required under paragraph (a) of this section and a copy of the summary required under paragraph (c) of this section.

(3) Field copy. The applicant must submit a field copy of the application that contains the technical section described in paragraph (d)(1) of this section, a copy of the application form required under paragraph (a) of this section, a copy of the summary required under paragraph (c) of this section, and a certification that the field copy is a true copy of the technical section described in paragraph (d)(1) of this section contained in the archival and review copies of the application.

(4) Binding folders. The applicant may obtain from FDA sufficient folders to bind the archival, the review, and the field copies of the application.

(5) Electronic format submissions. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

HISTORY: [50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 16668, Apr. 26, 1985; 50 FR 21238, May 23, 1985; 52 FR 8847, Mar. 19, 1987; 55 FR 11580, Mar. 29, 1990; 57 FR 17982, Apr. 28, 1992; 58 FR 47351, Sept. 8, 1993; 59 FR 13200, Mar. 21, 1994; 59 FR 50361, Oct. 3, 1994, as corrected 59 FR 60051, Nov. 21, 1994; 62 FR 40570, 40599, July 29, 1997; 63 FR 5233, 5252, Feb. 2, 1998; 63 FR 6854, 6862, Feb. 11, 1998; 63 FR 66378, 66398, Dec. 1, 1998; 63 FR 66632, 66670, Dec. 2, 1998; 64 FR 396, 401, Jan. 5, 1999, as confirmed at 64 FR 26657, May 17, 1999; 65 FR 56468, 56479, Sept. 19, 2000; 67 FR 9584, 9586, Mar. 4, 2002; 68 FR 69009, 69019, Dec. 11, 2003; 69 FR 18728, 18763, Apr. 8, 2004]

AUTHORITY: AUTHORITY NOTE APPLICABLE TO ENTIRE PART:

21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 371, 374, 379e.

NOTES: [EFFECTIVE DATE NOTE: 68 FR 69009, 69019, Dec. 11, 2003, amended paragraph (l), effective June 8, 2004; 69 FR 18728, 18763, Apr. 8, 2004, amended this section, effective June 22, 2004.]

NOTES APPLICABLE TO ENTIRE TITLE:

Cross References: Food Safety and Inspection Services, Department of Agriculture: See Meat and Poultry Inspection, 9 CFR CHAPTER III.

Federal Trade Commission: See Commercial Practices, 16 CFR chapter I.

U.S. Customs Service, Department of the Treasury: See Customs Duties, 19 CFR chapter I.

Internal Revenue Service, Department of the Treasury: See Internal Revenue, 26 CFR chapter I.

Bureau of Alcohol, Tobacco, and Firearms, Department of the Treasury: See Alcohol, Tobacco Production and Firearms, 27 CFR chapter I.

NOTES APPLICABLE TO ENTIRE CHAPTER:

[PUBLISHER'S NOTE NOTE: Nomenclature changes affecting chapter I appear at: 70 FR 40880, July 15, 2005.]

[PUBLISHER'S NOTE: For the uniform compliance date for food labeling regulations under Chapter 1, see 61 FR 67710, Dec. 24, 1996; 61 FR 68145, Dec. 27, 1996; 62 FR 49881, Sept. 23, 1997.]

NOTES APPLICABLE TO ENTIRE PART:

[PUBLISHER'S NOTE: For Federal Register citations concerning Part 314 Clarifications, see 62 FR 63268, Nov. 28, 1997.]

[PUBLISHER'S NOTE: Nomenclature changes affecting part 314 appear at 68 FR 24879, May 9, 2003; 69 FR 13716, 13717, Mar. 24, 2004.]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

AGENCY: Food and Drug Administration.

21 CFR Parts 71, 170, 171, 180, 201, 310, 312, 314, 330, 430, 431, 433, 510, 511, 514,
570, 571, 601, 812, 1003, and 1010

New Drug and Antibiotic Regulations

[Docket No. 82N-0293]

50 FR 7452

February 22, 1985

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revising its regulations governing the approval for marketing of new drugs and antibiotic drugs for human use. FDA is taking this action to speed up the availability of beneficial drugs to consumers by improving the efficiency of the agency's approval process for new drugs and antibiotic drugs, while improving the already high level of public health protection the drug approval and surveillance processes now provide. The improvements will help applicants prepare and submit higher quality applications and permit FDA to review them more efficiently and with fewer delays. This will benefit both consumers and applicants by permitting earlier availability and marketing of new drugs and antibiotics. This action is one part of a larger effort by FDA to review all facets of the agency's drug approval process.

DATES: These final regulations are effective May 23, 1985, except 21 CFR 314.80 *Postmarketing reporting of adverse drug experiences* is effective August 22, 1985. FDA will, however, accept applications until February 24, 1986 that are in the format required under either the current regulations or this final rule. For additional information concerning these effective dates see IV. "Paperwork Reduction Act of 1980" appearing in the preamble of this document.

FOR FURTHER INFORMATION CONTACT: Steve H. Unger, Center for Drugs and Biologics (HFN-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5220.

TEXT: SUPPLEMENTARY INFORMATION:

I. Introduction

This final rule completes the first phase of efforts by the Department of Health and Human Services (HHS) to revise Federal regulations governing the new drug approval process. This phase of the regulations (called the NDA Rewrite) finalizes new procedures in 21 CFR Part 314 for FDA review of new drug and antibiotic applications for marketing. This action completes the rulemaking process begun on October 19, 1982 (47 FR 46622). The second phase of these regulatory revision efforts (called the IND Rewrite) covers FDA procedures in 21 CFR Part 312 for reviewing investigational new drug applications. This second phase is nearing completion, following the publication of proposed regulations in the Federal Register of June 9, 1983 (48 FR 26720). A third phase of improving the drug approval process involves noncodified guidelines on application format and on fulfilling testing requirements. Together with other

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regulatory and administrative reforms, the IND/NDA Rewrite and related guidelines represent a major effort on the part of FDA to improve the entire process of drug approval regulation. This effort was begun by FDA through concept papers made available for public comment (*44 FR 58919*, October 12, 1979) and a related public meeting on November 9, 1979. It was accelerated and intensified at the request of the President's Task Force on Regulatory Relief.

The objectives of the NDA Rewrite final rule are to establish an efficient, but thorough, drug approval process in order both: (a) To facilitate the approval of drugs shown to be safe and effective; and (b) to ensure the disapproval of drugs not shown to be safe and effective. These regulations are also intended to improve FDA's surveillance of marketed drugs. Accordingly, the final regulations enable FDA to act as both a public health promoter, by facilitating the approval of important new safe and effective therapies, and as a public health protector, by keeping off or taking off the market drugs not shown to meet safety and efficacy standards.

In preparing the final rule, FDA carefully reviewed approximately 120 comments received from pharmaceutical manufacturers, trade associations, health professionals and professional societies, consumers and consumer organizations, and Congress. In addition, FDA held a series of meetings with agency employees in order to gain their views as part of the internal decisionmaking process. The agency also considered the recommendations of the Congressionally sponsored Commission on the Federal Drug Approval Process. In preparing the final rule, therefore, the agency has considered the views of virtually all persons having an interest in the drug approval process.

Like both the NDA and IND proposals, the NDA final rule has been reviewed by a special task force appointed by the Secretary of Health and Human Services, and chaired by the Commissioner of Food and Drugs, whose specific charge has been to review these regulations in accordance with Executive Order 12291 (*46 FR 13193*, February 19, 1981), the mandate of the President's Task Force on Regulatory Relief, and the policy objectives outlined above. Many of these issues were also reviewed by a separate FDA task force, which the Commissioner also chaired.

The NDA final rule is designed to complement the proposed IND regulations, especially in terms of fostering a continuous dialogue between FDA and applications throughout the drug development and approval process. For example, one of the major improvements over present practice suggested in the IND proposal was to allow any drug sponsor an opportunity to attend an "end-of-Phase 2" meeting with FDA officials in order to agree on a plan for Phase 3 clinical investigations. As stated in that proposal, FDA believes that such meetings can significantly shorten the period of subsequent NDA review. The IND proposal also encourages "Pre-NDA" meetings between FDA and applicants to discuss format and modes of presentation in the marketing application. These meetings will be especially necessary as applicants learn how to prepare marketing applications under the new format. As described further below, the NDA Rewrite final rule encourages such dialogue to continue throughout the NDA review period as well.

The new NDA regulations will be supplemented by a series of guidelines. These guidelines are intended to provide applicants with guidance on application format and on how to fulfill testing requirements. The format guidelines will address the overall summary and each of the different technical sections of the application. The guidelines on how to fulfill testing requirements will focus on the areas of animal toxicity testing and chemistry and manufacturing controls, as previously announced in the preamble to the IND Rewrite proposal (*48 FR 26720, 26721*). These guidelines are in addition to the overall 25 clinical guidelines that FDA prepared in the middle and late 1970's concerning the design of adequate and well-controlled studies on different classes of drugs. Finally, FDA plans to issue a guideline regarding the reporting of adverse drug experiences on marketed drugs, a draft of which has already been made available for public comment (*48 FR 4049*; January 28, 1983). FDA intends to continue to solicit public comment on draft guidelines before they are published in final form. For example, notices announcing the availability of several draft guidelines concerning how to fulfill chemistry and manufacturing controls requirements have already been published (see the Federal Register of February 1, 1984 (*49 FR 4040*) and May 7, 1984 (*49 FR 19412 and 19413*)). FDA hopes to have all these guidelines publicly available, at least in draft form, before the new regulations become effective, although the agency does not view the existence of draft or final guidelines as being a prerequisite for implementing this final rule.

The IND/NDA Rewrites and related guidelines are part of a larger, overall effort to improve the drug development and approval process. For example, FDA will continue to recognize the high priority given to new drug and antibiotic application reviews, to increase the efficiency in the management review of applications, and to strengthen the agency's scientific base. In addition, with the passage of the Orphan Drug Act of 1983, the agency's Office of Orphan Products Development is actively involved in facilitating the development of new drug and other products intended to treat rare diseases.

Highlights of this final rule, the agency's economic analysis, and responses to general comments are contained in the following introductory sections. The remainder of this preamble is devoted to a section-by-section analysis of comments received, responses to them, and contents of the final regulations.

II. Highlights of the Final Rule

As noted above, the guiding principle in the NDA Rewrite final rule is that the drug approval process should be efficient, but thorough, in order to facilitate the approval of drugs shown to be safe and effective, and ensure the disapproval of drugs not shown to be safe and effective. The regulations are also intended to improve FDA's surveillance of marketed drugs. In response to comments and further internal deliberations, the final rule has modified certain provisions of the proposal in order to meet these objectives better. The major provisions of the final rule are summarized as follows:

1. *Application format.* The final rule incorporates the proposed revisions designed to make the application format more amenable to efficient agency review. Thus, like the proposal, the new format requires an overall summary of the entire application and separate, detailed technical sections that each contain individual summaries and analyses of the specific information needed by the particular reviewing disciplines: clinical, pharmacology, chemistry, statistics, and biopharmaceutics (as well as microbiology for anti-infective drugs). The new format will therefore permit parallel review by each of the five (or six) disciplines. In addition, detailed technical sections that synthesize the important information about the drug will greatly facilitate review by agency officials. The final rule also provides applicants the option of submitting the chemistry section (if it is complete) 90 to 120 days prior to submission of the main application in order to expedite review and permit early resolution of deficiencies.

2. *Safety update reports.* The final rule also incorporates the general requirement contained in the proposal for applicants to submit new safety information learned about a drug while an application is being reviewed by FDA. The final rule modifies the timing and frequency of these reports in order to focus FDA evaluation of them at key points in the review process. Thus, under the final rule, safety update reports will be required 4 months following the initial submission of the application, following receipt of an "approvable" letter, and at other times upon FDA request. These safety update reports will ensure that approval decisions reflect the most up-to-date safety information available.

3. *Case report forms and data tabulations.* The final rule follows the general principle enunciated in the proposal that an efficient agency review of individual patient data should be based primarily on well-organized, concise, data tabulations, and that reliance on the more lengthy case report forms should be reserved for those instances where a more detailed review is necessary. Accordingly, the final rule provides: (i) That case report forms will be routinely required where the patient dropped out or died during a clinical study (because these forms are likely to disclose the most serious safety problems); (ii) that individual patient data tabulations will be required for the remaining patients; and (iii) that additional case report forms will be requested by FDA when needed to conduct a proper review of the application. In response to comments, the final rule clarifies that FDA reviewers, with the concurrence of the division director, will have access to whatever additional case report forms are needed to conduct a proper review. The preamble explains that this may include requests for full case reports from the most critical studies, but that these reports will ordinarily be requested early in the review process so as not to cause undue delay. These data submission requirements should promote a more focused, efficient review of the application without compromising the thoroughness of that review. FDA estimates that this approach will result in a 75 percent reduction, on average, in the number of case report forms now required to be submitted to the agency in order to obtain approval.

4. *Time frames for FDA review.* The final rule incorporates the time frames contained in the proposal pertaining to the agency's review of applications. Accordingly, the final rule gives the agency 180 days from receipt of an application to issue either an "approval" letter, an "approvable" letter, or a "not approvable" letter. This time period may be extended when major amendments are received, although the extension would only be for the extra time needed to review the amendments. The final rule, like the proposal, also defines the procedure and time frame for "filing" an application within the meaning of section 505(c) of the act (21 U.S.C. 355(c)). Codification of these time frames demonstrates the agency's commitment to reviewing applications promptly in accordance with the statutory mandate.

5. *Action letters.* The final rule also incorporates provisions contained in the proposal which clarify the meaning of its three action letters: approval letters, approvable letters, and not approvable letters. Like the proposal, the final rule clarifies that only an approval letter grants permission for marketing of a drug. In addition, the final rule adopts the proposed policy that the agency will issue an approval letter, rather than an approvable letter, when the only deficiencies in

the application concern editorial or other minor changes in the labeling, with approval conditioned on the deficiencies being corrected, as requested, before the drug is marketed.

6. *Foreign data.* The final rule incorporates the proposed policy that an application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved by FDA if: (i) The foreign data are applicable to the U.S. population and U.S. medical practice; (ii) the studies have been performed by clinical investigators of recognized competence; and (iii) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. These criteria assure the quality of any drug products so approved, while at the same time removing the need to conduct repetitive clinical testing in this country in those instances where adequate data have been generated abroad.

7. *Communication between FDA and applicants.* The final rule greatly expands upon the proposed provision concerning communication between FDA and applicants. The final rule, with greater emphasis than the proposal, encourages dialogue between FDA and applicants about scientific and medical issues that arise during the review process. This includes notifying applicants of easily correctable deficiencies found in an application shortly after those deficiencies are discovered, providing an opportunity for an informal meeting mid-way through the review process and again after FDA's review is completed, and expressly permitting telephone calls and other informal meetings as the need may arise. This provision builds on portions of the IND Rewrite proposal that encouraged such communication during the testing phase of the drug development process.

8. *Dispute resolution.* The final provision on dispute resolution has been significantly revised in order to build upon the general principles noted above with respect to communication between FDA and applicants. For administrative and procedural issues, the final rule establishes an ombudsman whose function will be to investigate what has happened and to facilitate a timely and equitable resolution. For scientific and medical disputes, the final rule provides that applicants should seek resolution through an "end-of-review conference" with appropriate agency staff and management representatives, and at other informal meetings as the need may arise. The final rule also provides for the participation of outside experts at these informal meetings when feasible. This procedure supersedes the appeals process described in the NDA (and IND) Rewrite proposals because that process was seen as being too formal and was not effective during the pilot period.

9. *Supplements.* The final rule, like the proposal, establishes different categories of supplements to approved applications concerning manufacturing and controls changes. The rationale for the categories is that changes that could affect the safety or effectiveness of a final drug product should be preapproved by FDA, but that other changes may be implemented by a firm while notifying FDA either concurrently or in the next annual report. Although some changes have been placed in different categories than originally proposed, the final rule should still result in a 20 percent reduction in the number of manufacturing and controls supplements that require prior approval by the agency. Thus, the final rule will enable drug manufacturers to implement some kinds of manufacturing changes significantly more promptly without compromising drug safety and effectiveness.

10. *Postmarketing surveillance.* The final rule modifies the proposal in several ways in order to focus FDA review more directly on the more serious adverse drug experiences. Under the final rule, 15 working day "alert reports" will be required for all adverse drug experiences that are both serious and unexpected, and for any significant increase in frequency of an adverse drug experience that is both serious and expected (rather than only unexpected fatal and life-threatening experiences, as had been proposed). Other adverse drug experiences, as specified in the final rule, will be required to be reported at quarterly intervals in the first 3 years following approval, and annually thereafter. The quarterly reporting requirement reflects the fact that close surveillance of a new drug's side effects is especially important during the first 3 years of marketing. Although the quarterly/annual reporting of adverse drug experiences is less frequent than the proposed period of 30 working days, FDA believes that such quarterly/annual reporting is consonant with the agency's need to review reports of expected or nonserious adverse drug experiences.

III. Economic Analysis

The agency has examined the economic consequences of these regulations in accordance with Executive Order 12291 and the Regulatory Flexibility Act. A final regulatory impact analysis has been prepared and placed in file with the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

The regulations are expected to shorten the total elapsed time required to approve the average application, including resubmission, from about 27 months to 21 months -- an average savings of 6 months. The average approval time for applications involving important new chemical entities is projected to improve from about 19 months to 17 months -- an average savings of 2 months. The faster approval and smaller savings for new chemical entities reflect the special priority already accorded these applications. Faster approvals for applications would benefit both consumers and pharmaceutical manufacturers. Consumers would have earlier access to important new drugs that have the potential to extend life, avoid hospitalization, or provide other significant health benefits. Firms developing new drugs would realize faster return on their research investments, thereby encouraging further investment in subsequent pharmaceutical research. The regulatory impact analysis examines some measures of these various benefits, although none are amenable to simple quantification in monetary terms.

Nonetheless, these benefits are substantial. For example, a 2-month speed-up in the approval of 15 therapeutically significant applications per year would result in about 500,000 additional prescriptions for these important drugs in the first year following FDA approval. The number of persons benefiting from these additional prescriptions would probably exceed 200,000, after adjusting the total for renewal and repeat prescriptions. Some of these individuals should receive very significant medical benefits such as avoidance of surgery, cure or stabilization of a life-threatening disease, or relief of a physical handicap. Many individuals should also save money as compared to alternate treatments.

The accelerated availability of new drugs to consumers will also increase industry revenues. However, the increase will not be as great as gross sales because some of the new drugs will displace less effective or more costly drugs.

Changes in the cost of the new drug application process itself will be minor. Increases include \$1.2 million annually for detailed NDA summaries, \$0.5 million annually for NDA safety update reports, and \$0.4 million annually for increased adverse experience reports for approved NDA's; decreases include \$0.4 million for less routine paperwork for NDA's, \$1.6 million for reduced supplements for approved NDA's, and \$1.6 million for reduced supplements for approved ANDA's. These latter two decreases relate to applications to change postmarketing manufacturing procedures for NDA's or ANDA's in minor ways. The net decrease of \$1.5 million is about \$1.0 million less than the cost savings estimated in the preliminary analysis, attributable primarily to cost estimates for safety update reports and adverse experience reports that were not calculated at the proposal stage.

The agency also concludes that these regulations will have a favorable impact on small firms because of cost savings associated with abbreviated applications, the type of application most frequently held by small firms. Due to the elimination of requirements for submitting certain postmarketing supplements, FDA estimates a savings of \$540 for each abbreviated application. While this impact is favorable, it will not be a significant savings for any one firm. Therefore, the agency certifies, in accordance with the Regulatory Flexibility Act, that this rule will not have a significant economic impact on a substantial number of small entities.

IV. Paperwork Reduction Act of 1980

In accordance with the Paperwork Reduction Act of 1980 (44 U.S.C. Chapter 35), the reporting and recordkeeping requirements in §§ 314.50, 314.55, 314.70, 314.71, 314.72, 314.80, 314.81, 314.90, 314.110, 314.120, 314.126, 314.200, 314.300, and 314.420 in these regulations will be submitted for approval to the Office of Management and Budget (OMB). Interested persons desiring to submit comments on the collection of information requirements pursuant to the Paperwork Reduction Act and its implementing regulations (5 CFR Part 1320) should direct them by April 15, 1985, to the Office of Information and Regulatory Affairs, OMB, Rm. 3002, New Executive Office Bldg., Washington, DC 20503, Attn: Bruce Artim. These requirements will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the Federal Register prior to May 23, 1985.

V. Comments on Proposed Rule

General Comments

1. FDA received approximately 120 comments on the proposed rule. These comments were received from pharmaceutical manufacturers, trade associations, health professionals and professional societies, consumer and consumer organizations, and Congress. A number of the proposed changes were generally supported by these diverse groups, especially those improving the application format, establishing time frames for FDA review of applications, and requiring safety update reports for pending applications. Other items considered especially beneficial by consumers included the

requirement for a description of the foreign marketing history of the drug and the proposal concerning postmarketing surveillance. In addition, industry comments found especially beneficial the adoption of a single set of regulations for both antibiotics and nonantibiotic drugs, the reductions in supplements and other reports, and the clarified definitions and procedures for FDA's issuance of action letters.

2. The major concerns raised by consumers and consumer organizations was the fear that two of the proposed changes could possibly result in the marketing of drugs that are not safe or effective, as required by law. The issues of concern in this regard were the proposal to eliminate the routine submission of most case report forms, and the proposal concerning the acceptance of foreign data.

FDA shares the view that any changes made in the new drug regulations should not in any way lower the safety and effectiveness of marketed drugs, and FDA has carefully reviewed each section of the final regulations to ensure that that result does not occur. With respect to case report forms, the final rule ensures that FDA reviewers will have access to any case report forms necessary to conduct a proper review of the drug's safety and effectiveness. With respect to foreign data, FDA carefully reviewed its proposed policy, and explains in this preamble why the agency does not believe that fears about a possible lowering of drug quality are warranted. The agency intends to administer the policy with this concern in mind. Both of these issues are discussed in more detail in the section-by-section analysis.

3. Comments received from the pharmaceutical industry raised three kinds of objections. First, industry comments believed that the proposed regulations were deficient in not addressing several areas that the industry believes are important, such as granting sponsors a right to bring disputed matters to an outside advisory committee, providing an ombudsman to resolve minor procedural disputes, expanding communication between FDA and applicants, and codifying substantive provisions of the standards for safety and effectiveness.

Second, industry comments suggested that, although many of the proposed revisions represented movement in the right direction, FDA should make more dramatic changes in the drug approval process in order to achieve adequate regulatory reform. For example, some industry comments urged replacing both case report forms and detailed tabulations with briefer summaries, placing even greater reliance on foreign data and requiring many fewer supplements to approved applications.

Finally, while agreeing with the concept of strengthened postmarketing surveillance, industry comments generally stated that the specific reporting requirements proposed were excessive and did not provide a corresponding public health benefit. These comments stated that the reporting requirements should be better tailored to the relative importance of the adverse drug experiences involved.

In response to these comments, FDA has added to the final rule major sections on communication between FDA and applicants and on dispute resolution, including establishment of an ombudsman. The final rule also contains a detailed statement on the agency's use of advisory committees, although the agency has not provided, for the reasons stated in that discussion, applicants with rights to advisory committee reviews of issues. With respect to codifying substantive standards for safety and effectiveness, FDA believes that current statutory and regulatory provisions contain the necessary flexibility to administer these provisions to the wide variety of drugs subject to FDA's approval authority. The agency has, moreover, undertaken to provide further guidance with respect to the efficacy standard through the publication of guidelines for over 25 classes of drugs. Finally, in the IND Rewrite proposal, FDA stated its intent to make "end-of-Phase 2" meetings available for all IND's. These meetings provide a mechanism for agency reviewing officials and sponsors, with input from outside experts, to agree on an overall plan for Phase 3 investigations and the objectives and design of particular studies necessary to demonstrate the safety and effectiveness of the drug. (See 48 FR 26732.) FDA believes that this in-depth, case-by-case approach, will greatly facilitate the drug development process by providing sponsors with specific information about safety and effectiveness requirements in a timely manner.

Second, FDA generally disagrees with the industry comments that suggested that specific provisions in the proposal did not go far enough in providing regulatory relief. As described further below, FDA believes that case report forms and tabulations provide information, viewed as necessary, that may not be obtained through summaries alone; that further changes in the foreign data policy are not now appropriate; and that significant further changes in the area of supplements could possibly adversely affect the assurance of FDA regulation of marketed drugs.

Finally, FDA agrees that improvements in postmarketing surveillance should focus high priority reporting requirements on the more important adverse drug experiences. Accordingly, as described further below, the final rule provides for more stringent reporting requirements for adverse drug experiences that are both unexpected and serious, and less stringent requirements for the others.

4. Several comments urged FDA to adopt more specific and detailed regulations that give clear guidance to the regulated industry and to FDA personnel. According to these comments, these regulations should include detailed requirements for FDA actions, broad admonitions about normative conduct, requirements for agency documentation of decisions, and internal review mechanisms. Comments objected to FDA relying upon guidelines, internal manuals, memoranda, and other similar informal mechanisms to handle practices and procedures because they are too imprecise, subject to change, and of questionable authority. However, if FDA does decide to rely heavily on staff manual guides, one comment urged FDA to establish and codify a policy stating that such guides are binding upon the agency.

Many comments addressed further the issue of guidelines. Several comments argued that it was hard to discern the proposal's true impact without reviewing the guidelines FDA intends to use to implement the regulations and, accordingly, that FDA should reopen the administrative record once the guidelines are available. Moreover, these comments believe FDA should limit the use of guidelines to those situations where negotiation and alternative methods are clearly necessary or desirable, such as in clinical trials of different diseases. Several comments also asked FDA to provide notice and comment procedures on draft guidelines and staff and compliance manuals before final ones are prepared. Finally, some comments objected to FDA's reliance on guidelines because such documents often remain internal working documents and, according to these comments, are applied less consistently than the regulations. Finally, one comment urged that the final rule, or another proposal, should address procedural issues in the application review process, such as the designation of a primary review team early in the process, the need for meetings, concurrent review of an application by members of a review team, the finality of each part of the review once it is completed, and the importance of a tracking system to determine the history and current location and status of all submissions to FDA.

FDA believes its proposal provided adequate notice of the rights and responsibilities of both applicants and the agency in the drug approval process. FDA believes the more detailed regulations urged by these comments would add very little to the structure of the new drug approval process provided by FDA's combination of regulations, guidelines, and staff guides, while making the process more inflexible and difficult to change. The agency believes the proposal struck a proper balance between the need for regulatory requirements, the use of guidelines to help persons comply with those requirements, and the use of staff manuals to direct agency employees. FDA recognizes that the prompt issuance of clear guidelines will be most helpful to applicants and, thus, the agency is taking steps to expedite the development of guidelines and to clarify for its staff the role of guidelines in the regulatory process. Because FDA recognizes the significant contribution the industry, the medical community, and other members of the public can make to the development of scientifically sound guidelines, the agency routinely solicits comments on its guidelines either as draft or as final documents. With respect to the guidelines developed to implement this final rule, FDA intends to issue them as draft guidelines and to seek comments on them before they are made final. FDA believes it has provided adequate notice for this rulemaking proceedings and does not intend to reopen the administrative record on the regulations after the guidelines (or draft guidelines) are issued. Finally, FDA believes that administrative steps short of codification, such as staff manual guides, are appropriate for many management issues.

5. Several comments suggested that FDA implement many of its proposed procedural improvements in the new drug approval process immediately following the closing of the comment period (for example, changes in the content and format of an application, time frames for filing and reviewing an application and amendments, provisions on communications between the agency and applicants, and procedures for action letters).

Although FDA implemented several changes at the time it published the proposal (i.e., implementation of the informal appeals process; changes in the procedures for submitting samples; and the policy to notify applicants about deficiencies in chemistry, manufacturing, and controls information within 90 days of the beginning of the review of an application), the agency believes there is insufficient justification to implement other new requirements in advance of traditional effective date periods. FDA also notes that certain changes in the regulation (such as the procedures for action letters) simply codify current practice and so that immediate implementation of the final rule would not have had measurable impact.

6. One comment suggested that FDA impose user fees on industry for services FDA performs, particularly the costs of on-site inspections of domestic and foreign facilities. Another comment suggested that the agency incorporate into a final rule requirements for the evaluation of important new drugs in children before or at the time of approval of the application.

FDA believes these complex issues are sufficiently unrelated to the regulatory improvements in the new drug approval process that are implemented by the final rule that full consideration of them now would unnecessarily delay

implementation of the rule. The agency is, however, exploring each of these issues separately and welcomes further discussion of them.

Effective Date

7. FDA received several comments recommending various effective dates for the final rule. Several comments suggested an effective date for the final rule of 180 days or 1 year, but also suggested that FDA accept applications up to the effective date in either the old, proposed, or new formats. A medical association suggested that FDA clarify how the regulations will apply to studies already in progress and to studies completed but not submitted before the effective date of the regulations. Finally, one comment urged that FDA not issue a final rule amending its new drug application regulations until after it has published and received comments on its proposal to revise the investigational new drug regulations.

FDA has concluded that these final regulations will become effective May 23, 1985, except § 314.80 *Postmarketing reporting of adverse drug experiences* will become effective August 22, 1985. FDA will, however, accept applications until February 24, 1986, that are in the format required under either the current regulations or this final rule. The separate effective date for the reporting of adverse drug experiences reflects the time FDA believes applicants may need to adapt to the new regulations. As noted above, with respect to application format, FDA has followed the suggestion to permit applications to be submitted in the format prescribed by either the current regulations or this final rule (but not the proposed rule). This 1-year period also covers the submission of case report forms and data tabulations. FDA believes this 1-year period of optional formatting will facilitate a smooth transition from the old to the new regulations. Within the parameters described above, the effective dates apply to studies in progress or not yet submitted to FDA.

Although FDA will accept for 1 year applications in the format required under the current regulations, the substantive requirements of the regulations will apply to pending and approved applications on and after May 23, 1985 under this final rule. For example, the requirements and procedures for amendments, communication between FDA and applicants, dispute resolution, withdrawal by the applicant, safety update reports, supplements, records and reports, time frames for FDA action, action letters, adequate and well-controlled studies, and withdrawal of approval will apply after 90 days to all applications regardless of the format in which they appear.

Finally, in the Federal Register of June 9, 1983 (48 FR 26720), FDA proposed to revise its regulation governing the investigational use of new drugs. The comment period on the proposal closed August 8, 1983, and the agency is reviewing those comments. FDA does not believe that the IND rulemaking proceeding should further delay these final regulations because the two sets of regulations address different stages of the new drug development and approval process, and can be implemented separately in a satisfactory manner.

8. FDA has added to the final rule a new section that states the agency's intention that the regulations be applied in a manner that facilitates the approval of safe and effective new drugs, ensures that drugs not shown to be safe and effective are not marketed, and provides for an effective system for FDA's surveillance of marketed drugs.

Definitions (§ 314.3)

9. Several comments objected to the agency's proposed definition of the term "drug substance," claiming that the definition is overbroad and would wrongly subject the following to FDA regulation as new drugs: foods, vitamins, minerals, amino acids, other nutritional substances, and intermediates used in the synthesis of the drug substances.

FDA does not believe that the proposed definition of "drug substance" has the broad reach attributed to it by the comments. The proposed definition does not subject substances to FDA regulation as new drugs that do not fall within the definition of "new drug" in section 201(p) of the act (21 U.S.C. 321(p)). Moreover, the proposed definition is consistent with the definition of "drug" in section 201(g)(1) of the act and the agency's definition of "active ingredient" in § 210.3(b)(7) (21 CFR 210.3(b)(7)) of FDA's current good manufacturing practice regulations. FDA has, however, revised the definition in the final rule to make clear that it does not apply to intermediates used in the synthesis of the drug substance.

Application Form (§ 314.50(a))

10. One comment suggested that the proposed changes in the format for an application, under which a reviewer would receive only an overall summary and a technical section devoted to the reviewer's own discipline, would make it harder for a reviewer to consider relevant data that appear only in another reviewer's technical section.

The new application format should not have the result suggested by this comment. The application summary is intended to provide reviewers with adequate information about subjects outside their own review disciplines. Moreover, reviewers will also have access to other technical sections in the archival copy of the application, which will be maintained as a reference copy in the reviewing division's document room. Thus, reviewers will have access to whatever data they need for their reviews.

11. Several comments suggested that the regulations should make it clearer that the revised new drug and antibiotic application form is intended to serve essentially as a check list of basic information about the new drug and the application.

FDA agrees that the application form should serve only as a capsule listing of the contents of the application and the most basic information about the drug. This purpose will be self-evident from the revised form itself and, for that reason, no changes in this regard have been made in the regulations.

12. One comment objected to the requirement that the application form contain the established name, proprietary name, and code of the drug product. The reason for the objection was that some of the information may not yet exist when the application is filed. Two comments also sought clarification of the term "code" and asked whether it referred to the chemical name, shipping code, or marketing code.

The reason that names and codes used for the drug product must be submitted on the application form is to provide reviewers with easy identification of the product formulations to which the application refers. The term "code" would apply to any designation of a drug that would help identify it. To the extent one of the listed identifiers is not available, it would not need to be provided.

13. One comment suggested that the agency should establish procedures providing for the early submission and review of the chemistry, manufacturing, and controls section and/or the preclinical data section before submission of the clinical data and other sections. According to the comment, these early submissions would expedite ultimate approval by permitting early review and resolution of deficiencies in these technical areas.

FDA has revised the final rule (to be elaborated on by a staff manual guide) to provide for the early submission of chemistry, manufacturing, and controls information, at the option of the applicant. During the IND period, applicants will be permitted to submit information about fully developed chemistry, manufacturing, and controls procedures and specifications 90 to 120 days in advance of the submission of the main application. Chemistry, manufacturing, and controls submissions would not be accepted less than 90 days before the submission of the main application, as they would come too late to improve the speed of the review process significantly. Similarly, such submissions would not be accepted more than 120 days before submission of the main application because they would be premature and would likely not be sufficiently complete or final for review purposes. (Because review of preclinical data is not a common source of delay in the review process, the final rule does not provide for their early submission.)

The final rule expands upon past practice which had been to limit such early submissions only to drugs offering therapeutic advances. The agency notes, however, that in expanding the permissibility of such early submissions to other drugs, FDA's ability to review them early will depend upon available resources. Full applications are viewed as having higher priority, as are early submissions of chemistry, manufacturing, and controls information for drugs offering therapeutic advances. Nevertheless, this change in the final rule provides a mechanism for speeding the review of at least some applications for which a mechanism does not presently exist.

14. One comment suggested that FDA clarify the status of its paper NDA policy in the final rule.

FDA has revised the final rule to include a description of the "paper NDA." This is an application for a duplicate of a marketed drug product which relies primarily on published literature to provide substantial evidence of effectiveness and adequate scientific evidence of safety for the claimed indications. A complete description of FDA's paper NDA policy appears in the Federal Register of May 19, 1981 (46 FR 27396).

Summary (§ 314.50(c))

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15. Several comments endorsed the requirement for an overall summary, but urged that it should resemble more a brief summary than a lengthy treatise.

FDA agrees in part. As stated in the proposal, the summary is intended to facilitate review of the application. If a more complete summary of any specific section of the application is needed to provide the necessary information for review purposes, it should appear in the appropriate technical section. FDA also will not refuse to file an application or delay its approval if the summary is inadequate, provided the data contained in the technical sections of the application show that the drug is safe and effective. Applicants should recognize, however, that a superficial, poorly written, or incomplete summary will not serve its intended function of facilitating review and could even prolong the review process if it is confusing. The summary, therefore, should include critical details of study design, sufficient numerical data (tabular or graphic) to provide a quantitative understanding of the data, and a forthright discussion of any problem areas. Although the preamble to the proposal suggested that a typical summary should be 50 to 200 pages long, length will likely vary according to the nature of the drug and the quantity and type of information available. Fifty pages should not be viewed as a minimum requirement, nor 200 pages a maximum; applicants should instead be guided by the circumstances surrounding the particular application at hand.

16. FDA received several comments concerning the proposed requirement that the overall summary contain a fully annotated copy of the draft labeling. One comment asked that FDA require annotations to drug labeling only for claims about safety and effectiveness. Another comment asked for clarification about how omissions from labeling should be annotated. The comment also objected to the requirement that the labeling bear annotations to the information in both the summary and the technical sections of the application, suggesting that such a requirement is redundant. A third comment suggested that the summary should contain only a brief summary of the labeling information about the drug, and that copies of the labeling itself (including labels, packages, and package inserts) should not be required. Finally, one comment found the proposal unclear about whether labeling should be included in the clinical or chemistry sections of the application, and whether reviewers would receive copies of labeling.

Assessment of the adequacy of labeling is a critical part of FDA's review of a new drug application. In determining whether the data and information in an application support the claims made in the product's labeling, it is helpful to know the precise information that the sponsor considers supportive. By providing reviewers with an annotated copy of the proposed labeling for the drug, and by directing the reviewer to both the summarized and detailed data supporting the labeling, the sponsor can assure that critical supporting data are not ignored and that confusion (with its inevitable delay) about the basis for labeling does not arise.

As indicated, FDA believes that annotations referring to both the technical sections and the overall summary will best facilitate review. The inclusion of annotations to the summary will be particularly important to the reviewers who do not receive the technical sections, and to others, such as FDA's managers and advisory committee members, who will not review all of the technical data. These reviewers also may wish to consider certain matters in detail, however, and the references to technical sections will facilitate this. By law, "specimens" of the labeling are required to be submitted, and brief summaries, as suggested by one comment, are not viewed as adequate. The agency's guideline on preparing a summary will clarify more fully the kinds of information that should appear in annotated labeling, and how omissions from the labeling should be annotated.

Finally, an annotated copy of the labeling will appear in the summary, which will be provided to each reviewer. In addition, copies of labels and other labeling pieces will be contained in the archival copy of the application where they will be available to all reviewers, as necessary.

17. One comment supported FDA's proposal to use the application summary to prepare the summary basis of approval (SBA) document that is made publicly available following approval of the application. Another comment suggested that FDA work with the applicant during the preparation of the SBA and allow the applicant to review the SBA before it is released to ensure the protection of proprietary information.

Although FDA believes applicants can play a large role in the development of the SBA through the preparation of the summary, the SBA necessarily reflects FDA's judgment, and not the applicant's, of what data and information in the application support approval of the drug product. FDA believes that an applicant's review of the SBA to identify proprietary information is unnecessary because FDA has traditionally not included such information in the SBA.

18. One comment suggested that applicants should not ordinarily be required to submit a completely revised summary with a resubmitted application, and should be permitted, to the extent possible, to submit only an addendum to the original summary.

FDA agrees that an addendum to a summary is appropriate if minor changes are made to an application. Significant submissions, however, such as providing additional data in response to a "not approvable" letter, would necessitate a revised summary that again reflects a clear and concise description of the information in the application.

19. One comment asked FDA to clarify its requirement for the "marketing history" of a drug by other persons.

This requirement is limited to the marketing of the drug outside of the United States, and it is intended that it will be met with brief information concerning where and when the drug has been marketed, for what indications, and any significant safety or effectiveness problems that developed during such foreign marketing. The agency has revised this provision to require also a list of countries in which applications for marketing are pending. This information will facilitate FDA contacts with foreign drug regulatory officials about the drug.

Chemistry, Manufacturing, and Controls Section (§ 314.50(d)(1))

20. FDA received several favorable comments concerning proposed changes in the chemistry section of the application. For example, one comment was pleased that the proposal generally reflected the format and level of detail of manufacturing and controls data required by the European Economic Community to market a drug product. Another comment agreed with FDA's proposal to eliminate requirements for information available to the agency under its current good manufacturing practice (CGMP) regulations, stating that this change will substantially lessen the burden of preparing an application without compromising safety or effectiveness.

21. FDA received several comments regarding the agency's proposal to permit references in the chemistry technical section to compendial monographs. One comment urged FDA to go even further and not require detailed descriptions of drug substances subject to compendial monographs if the source of the substance is identified and CGMP's are followed in manufacturing it. A comment supported the proposal, believing that it reflects FDA's willingness to rely upon the compendia as authoritative sources of pharmaceutical quality standards. Two other comments suggested that the agency should also permit references to the Food Chemicals Codex, the British Pharmacopeia, and other compendia.

The agency is issuing this provision essentially as proposed, with one clarification. Although FDA believes that references to the official compendia may be relied upon under proper circumstances to provide required information, new developments in drug synthesis and advances in analytical technology may introduce new concerns about the chemistry of drug substances that are not adequately addressed by current compendial monographs. In those cases, FDA may need additional information about a drug substance to ensure that additives or byproducts of the synthetic process are properly controlled. Although a reference to official compendia will often satisfy the requirements, FDA has revised the final rule to state that FDA may require that additional information be submitted to permit the proper review of the application. This is particularly the case for tests for impurities and adulterants that might be present depending upon the source of material and the manner of processing the applicant employs. While compendial monographs are intended to assure the identity, strength, quality, and purity of the drug, they are not intended to include in each monograph a test for every impurity or adulterant. Thus, FDA concludes that additional information about drug substances subject to compendial monographs will sometimes be required.

The regulation limits the compendial sources that may be referenced to "official compendia" because a special relationship exists between FDA and the official compendia (United States Pharmacopeia/National Formulary) under the act, where FDA is authorized to enforce compendial standards (see section 502(g) of the act (21 U.S.C. 352(g)).

22. Several comments addressed the proposed requirements for documentation of raw materials and reagents used in the manufacture of the drug substance. One comment thought the requirements were ambiguous. A second comment criticized the proposal as continuing to require too much information about the method of synthesis, isolation, and purification of a drug substance. This comment suggested that either the regulations or a guideline should make it clear that an applicant need only submit such information that applies after a pivotal intermediate used to produce the drug substance is identified. Another comment asked for clarification of the requirement for the submission of specifications and analytical methods for components of a drug product (regardless of whether they appear in the finished product) and whether it includes raw materials used in the drug substance.

FDA believes that complete information about raw materials, reagents, in-process controls, and methods used in the manufacture of a drug substance are needed (particularly for a new chemical entity) to characterize fully the drug substance. The level of detail required, however, will vary according to the nature of the drug and FDA's familiarity with it. To provide flexibility, the regulation itself is general in nature, and FDA will prepare a guideline on the chemistry tech-

nical section to aid applicants in determining the appropriate level of data and information on a drug substance needed in a particular case.

23. One comment suggested that the agency should only require information about components of a drug substance that remain, in some measure, in the drug product or which could have an adverse effect on safety or effectiveness.

FDA disagrees with this comment. Information about components that do not appear in the finished drug substance or drug product is important in determining whether the specifications and analytical methods are appropriate to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of drug products made for it. This information is also important to assure batch-to-batch reproducibility of the drug substance. Although these components do not appear in the finished drug substance or drug product, they may, or changes in them may, significant affect the finished drug product.

24. Several comments suggested that the final rule should explicitly recognize current practice, under which applications may provide for alternative sources of inactive ingredients and alternative manufacturing procedures, including the following: (1) Reasonable alternatives for any material used in the synthesis of the new drug substance, (2) alternative methods or variations of methods of synthesis within reasonable limits which do not affect the characteristics of the substance, and (3) reasonable quantitative variations in the ingredients in the product.

FDA agrees with these comments, and has revised the final rule to provide for identifying such alternatives. Generally, an alternative method or variation should include a description of the circumstances under which the alternative or variation will be used. Comparable specifications and analytical data for the material produced by the alternative methods or variations must also be submitted.

25. Several comments addressed the inclusion of bioavailability-related information in the chemistry section. One comment objected to the addition of bioavailability to the statutory standards of identity, strength, quality, and purity -- standards that, according to the comment, adequately cover the physical and chemical parameters affecting bioavailability. The comment also pointed out that bioavailability is covered under its own technical section. Another comment objected to the requirement to provide specifications and analytical methods to ensure bioavailability because the methodology may not exist. A third comment suggested that references to the bioavailability of drug products made from a drug substance be deleted from the paragraph on the drug substance because it appears in the paragraph on the drug product.

FDA believes that these comments misunderstood the proposed requirements. The final rule, like the proposal, does not require the chemistry section of an application to contain information about the bioavailability of the drug product. That information is contained in the human pharmacokinetics and bioavailability section. What is required in the chemistry section is that an applicant provide specifications and analytical methods for the drug substance and the drug product that will assure the ultimate bioavailability characteristics of the drug product. For example, if the bioavailability of the drug product depends on the crystalline form of the drug substance used in the drug product, the chemistry technical section must contain the necessary specifications and analytical methods to ensure that the substance has the necessary crystalline form. This requirement for specifications and analytical methods pertains to both the drug substance and drug product, because specifications at either or both stages could be pertinent to bioavailability, but it does not apply to intermediates and raw materials used in the manufacturing of the drug substance. If specifications and methods are unnecessary for assuring bioavailability, they need not be supplied. Although it might be argued that the standard of "quality" adequately covers the physical and chemical parameters affecting bioavailability, there is no good reason not to be explicit about the requirements for information about drug chemistry that, although they pertain to bioavailability, must be evaluated by FDA's chemistry reviewers.

26. One comment suggested that the phrase "specifications related to stability" should be deleted from the requirements for the drug substance because expiration dates on drug substances are not required.

Like the previous comments on specifications relating to bioavailability, FDA believes this comment misunderstood the proposal. Although expiration dates for drug substances are not required, establishment of a specification for stability of the drug substance may in some cases be needed to assure the quality of the drug product. If there is no such specification, it need not be supplied.

27. One comment suggested that references to process controls should not be required because they are adequately regulated under the CGMP regulations. According to this comment, requiring this information in an application and requiring agency approval before changes can be made takes away manufacturers' flexibility for establishing procedures for in-process tests and for determining the significance of testing results.

The agency disagrees with this comment. FDA believes that a review prior to marketing of in-process controls is needed to determine whether appropriate tests and limits are established (for example, for solvents and particle size) which may affect physiological or pharmacological activity.

28. One comment urged that the agency codify its current policy that methods validations will not delay approval of an application.

FDA views itself as bound by its current policy, unless changed, regardless of whether it is included in the regulations. Moreover, the policy is of a type that the agency would more likely cast as a guideline, given its length and complexity, than as a regulation. In addition, the agency memoranda on this subject, which have been made public, adequately describe the policy and, thus, FDA does not believe that codifying the policy is necessary.

Nonclinical Pharmacology and Toxicology Section (§ 314.50(d)(2))

29. Several comments objected to FDA's proposal to require a description of studies of nonclinical pharmacological actions of the drug for possible therapeutic indications for which the applicant is not seeking approval. These objections are premised on the belief that the information would be irrelevant to the drug's proposed indications, that the requirement would delay submission of an application while the applicant gathered the information, and that time and effort of reviewers would be wasted, particularly if the information were to lead them to speculate about other potential, new indications.

FDA agrees in part with these comments, but believes the purpose of this section was not well described in the proposal. Information about pharmacological effects other than the primary effect related to the proposed use is not usually critical to evaluating the effectiveness of the drug, but these pharmacologic properties are pertinent to a full understanding of the drug's effects, e.g., they may help explain side effects and drug interactions. Such information also is pertinent to investigational use of the drug, so it should be unnecessary for an applicant to perform new analyses to meet the requirement. The agency has revised the final rule to make this requirement clearer.

30. Several comments addressed the form of submission of data from animal studies. One comment requested clarification as to whether the revised regulations are intended to continue the current practice under which individual animal data are only reported in tabulations, and the "raw data" (laboratory notebook, worksheets, and other documentation relating to individual animals) are not submitted unless FDA has reason to request them in a particular case. Another comment suggested that FDA require summaries instead of tabulated individual data from long-term toxicity and carcinogenicity studies in order to reduce the size of the application.

The nonclinical pharmacology and toxicity section of the application is intended to continue current practices with respect to the submission of individual animal data. Thus, applicants are not required to submit laboratory notebooks, worksheets, and other documentation relating to individual animals (although those materials are subject to record retention requirements under the good laboratory practice (GLP) regulations (21 CFR Part 58)). Although summaries that contain tabulations and graphs are helpful for describing long-term toxicity and carcinogenicity studies, FDA believes that full tabulations of individual animal data are necessary to conduct a proper review of these important safety-oriented studies.

31. Several comments questioned the implication in the proposal that all pharmacological studies are subject to the agency's GLP regulations. These comments noted that those regulations apply only to nonclinical safety studies and not to other animal studies, such as nonclinical pharmacology studies. Other comments suggested that the regulation should require only a description of "significant" deviations from the GLP regulations, or a "statement of differences" for studies that were not in "substantial" compliance with them.

FDA agrees that the proposal might be read to imply that all pharmacological studies are subject to FDA's GLP regulations. The agency has revised the final rule to clarify that an application is only required to contain a statement regarding compliance with GLP's for a "nonclinical laboratory study" as defined in 21 CFR 58.3(d). FDA, however, has not made the other suggested change. Because the GLP regulations describe minimum standards for nonclinical laboratory studies, FDA believes that it is appropriate that the application contains a description of deviations from those requirements. The agency advises that such studies may still be relied upon, depending on the nature of the deviations.

Human Pharmacokinetics and Bioavailability Section (§ 314.50(d)(3))